Spring 5-2004

Synthesis of 7-hydroxy-bicyclo[4.4.1]undeca-1,5-dien-11-one as a Precursor to the Synthesis of Ingenol

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Appendix E - UNIVERSITY HONORS PROGRAM
SENIOR PROJECT - APPROVAL

Name: Douglas Davis

College: Arts & Sci. Department: Chemistry

Faculty Mentor: Dr. David Young

PROJECT TITLE: Synthesis of 7-hydroxy-bicyclo[4.4.1]undeca-1,5-dien-11-one as a Precursor to the Synthesis of Ingenol

I have reviewed this completed senior honors thesis with this student and certify that it is a project commensurate with honors level undergraduate research in this field.

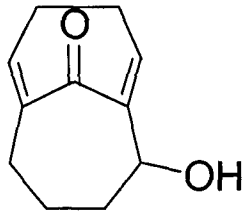
Signed: David S. Young, Faculty Mentor

Date: 5/4/04

General Assessment - please provide a short paragraph that highlights the most significant features of the project.

Comments (Optional):

Synthesis of 7-hydroxy-bicyclo[4.4.1]undeca-1,5-dien-11-one as a Precursor to the Synthesis of Ingenol



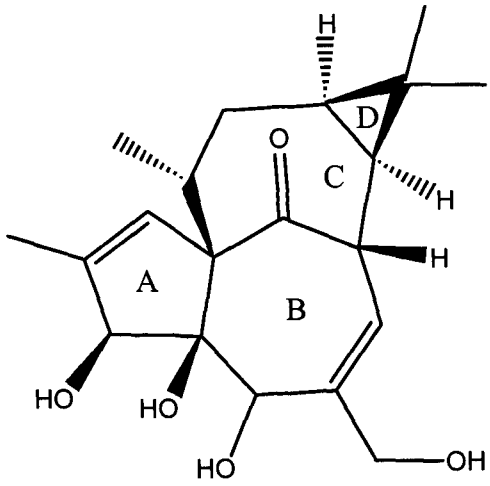
Douglas Davis
Faculty Mentor: Dr. David Young
May 3, 2004

In partial fulfillment of the requirements for the Honors Program and the Honors Chemistry Degree

Background of Ingenol

Ingenol (**1**) was first isolated in 1968 from the African plant *Euphorbia ingens*. Its tetracyclic structure was determined by X-ray crystallography [1,2]. Ingenol and its various derivatives have shown tumor promoting as well as anti-cancer and anti-HIV activity, and this has led to great interest in the synthesis of ingenanes. The synthesis of the molecule is complicated by the unique stereochemistry of the strained B,C ring system with its trans intrabridgehead stereochemistry. Recently, two total syntheses of ingenol have been published [3,4].

Figure 1. Ingenol



1

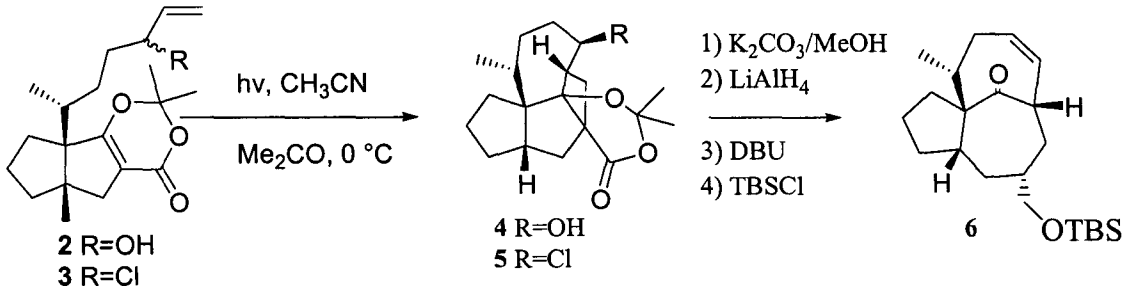
The direct purpose of this research is to examine new methods for constructing the B,C ring system of the ingenol skeleton. The hope is that this will serve as a basis for a shorter total synthesis of **1**. The two previous syntheses relied on a ring rearrangement in order to arrive at the desired structure. We are hoping to use an ene-yne methathesis to

form the C ring and a combination of the Favorskii and Cope rearrangements to form the B ring.

Previous Syntheses

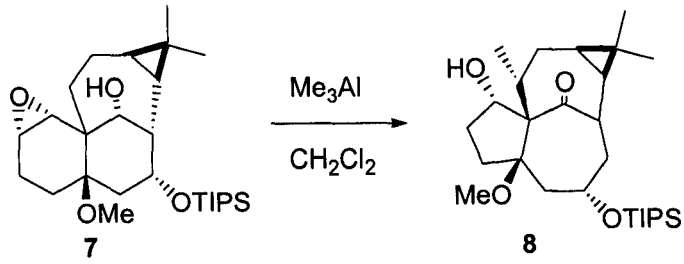
The formation of the desired B,C ring system as performed by Winkler, et al. in the first total synthesis is shown in Figure 2. Initially, the use of **4** was planned for this ring rearrangement but the yields of the previous step from **2** were low (16%). It was found that **5** could be made by the photocycloaddition of **3** in 60% yield. **5** underwent a fragmentation, followed by a reduction, the elimination of Cl, and the silylation of the resulting alcohol to produce **6** in a 35% yield. This yielded a stereochemically correct A,B,C-tricyclic core.

Figure 2. Formation of the A,B,C ring system of Ingenol by Winkler et al.



The synthesis by Tanino et al. uses a Lewis acid mediated ring rearrangement. However, they were able to make the entire A,B,C,D tetracycle (Figure 3) from **7** using trimethylaluminum and methylene chloride as a solvent to give **8** in 76% yield.

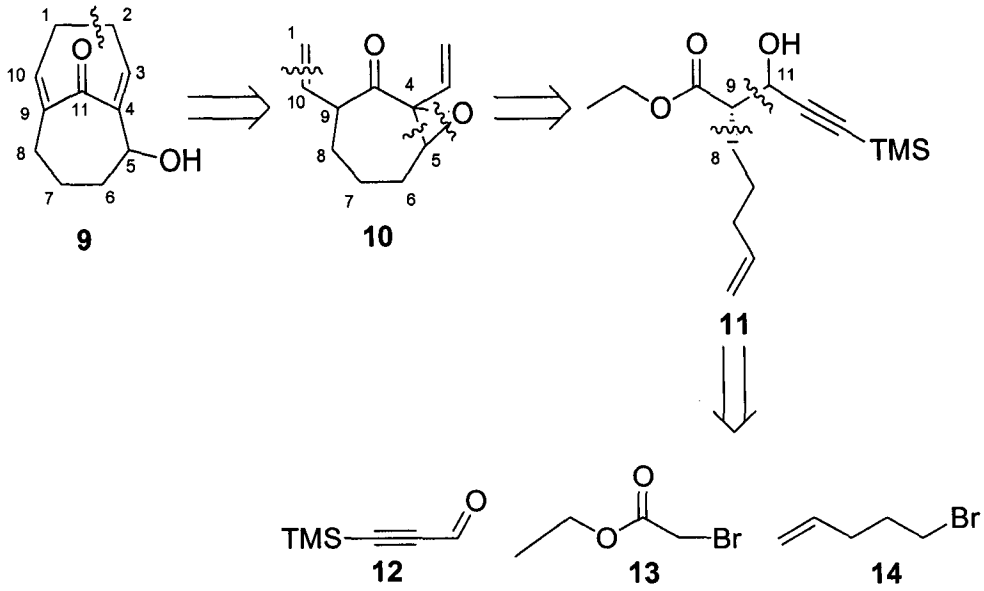
Figure 3. Formation of the A,B,C,D ring system of Ingenol by Tanino et al.



Retrosynthetic Analysis

Scheme 1 details the retrosynthetic analysis of the target molecule, 7-hydroxy-bicyclo[4.4.1]undeca-1,5-dien-11-one (**9**), using our method. Disconnection of the C_1-C_2 bond leads to **10**. Removal of the epoxide spanning C_4 and C_5, cleavage of the C_4-C_5 bond through metathesis, and disconnection of C_1 yields **11**. Cleavage of the C_9-C_{11} and C_9-C_8 bonds leads to the three staring materials, **12**, **13**, and **14**. Dr. Young's group has already accomplished the preparation of **12** while **13** and **14** are available for purchase commercially.

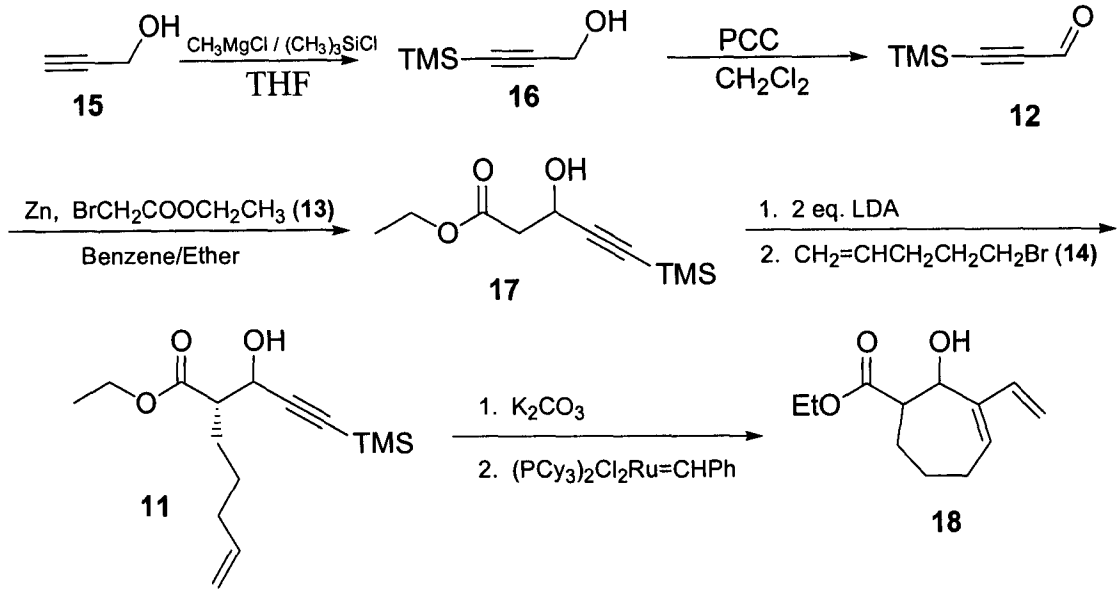
Scheme 1. Retrosynthetic analysis of the target molecule



Proposed Synthesis

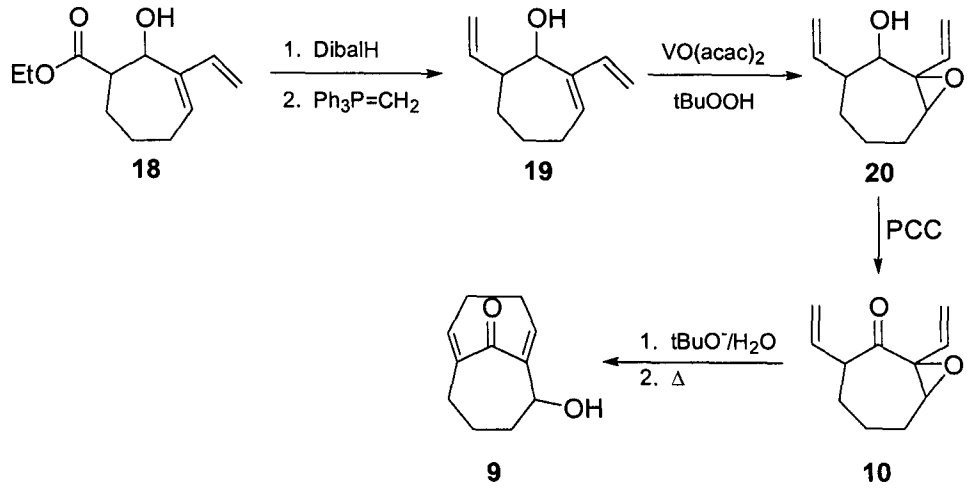
In Scheme 2, propargyl alcohol (**15**) is first silylated using trimethylsilyl chloride in THF and is then oxidized with PCC to form the trimethylsilyl propargyl aldehyde, **12**. The addition of **13** is accomplished first by metallation of the C-Br bond using activated zinc [5] and then by subsequent addition to the aldehyde to yield **17**. Two equivalents of lithium diisopropylamide (LDA) are used to remove the acidic hydrogens so that the enolate ion that is formed can undergo alyklation with the primary halide, **14**, to produce **11**. The removal of the TMS group is accomplished using potassium carbonate and the ring-closing metathesis is accomplished using Grubbs' catalyst to yield **18**.

Scheme 2. Proposed synthesis of the first ring of the target molecule



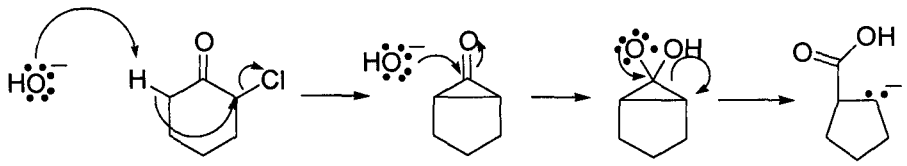
DibalH is used to reduce the ethyl ester group of **18**, and the resulting aldehyde undergoes a Wittig reaction to produce **19** (Scheme 3). The endocyclic double bond is epoxidized using $VO(acac)_2$ and tert-butyl hydro-peroxide to give **20**. The secondary alcohol is then oxidized to a ketone using PCC. It is hoped that **10**, when heated in the presence of tert-butoxide, will undergo a tandem Favorskii-Cope rearrangement to yield the desired product, **9**.

Scheme 3. Proposed synthesis of the second ring of the target molecule



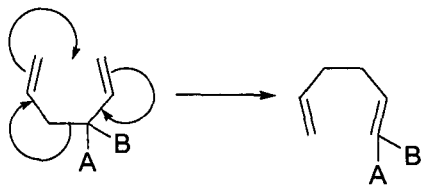
In the Favorskii rearrangement, an α-halo ketone six-membered ring rearranges to a five-membered ring. This is accomplished by first deprotonating the α-hydrogen of the carbon on the opposite side from the halogen with a bulky base. The enolate ion attacks and the halide leaves to form the unstable cyclopropanone. The base then attacks the carbonyl carbon breaking the double bond to oxygen. When this double bond reforms, it can break one of the carbon-carbon bonds due to the ring strain. This gives the desired ring contraction product (Figure 4).

Figure 4. Mechanism of Favorskii Rearrangement



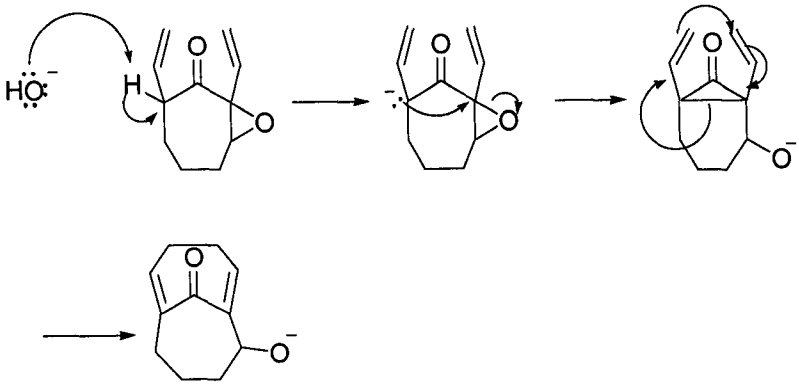
In the Cope rearrangement a 1,5-diene undergoes a 3,3 sigmatropic rearrangement. This is usually initiated by heat (Figure 5).

Figure 5. Mechanism of the Cope Rearrangement



It is anticipated that the α-hydrogen of the ketone (**10**) will be deprotonated to form the enolate ion. This enolate ion would then attack the epoxide ring to give the cyclopropanone. It is projected that the resulting molecule would then undergo a Cope rearrangement to give **9** (Figure 6).

Figure 6. Favorskii-Cope tandem rearrangement

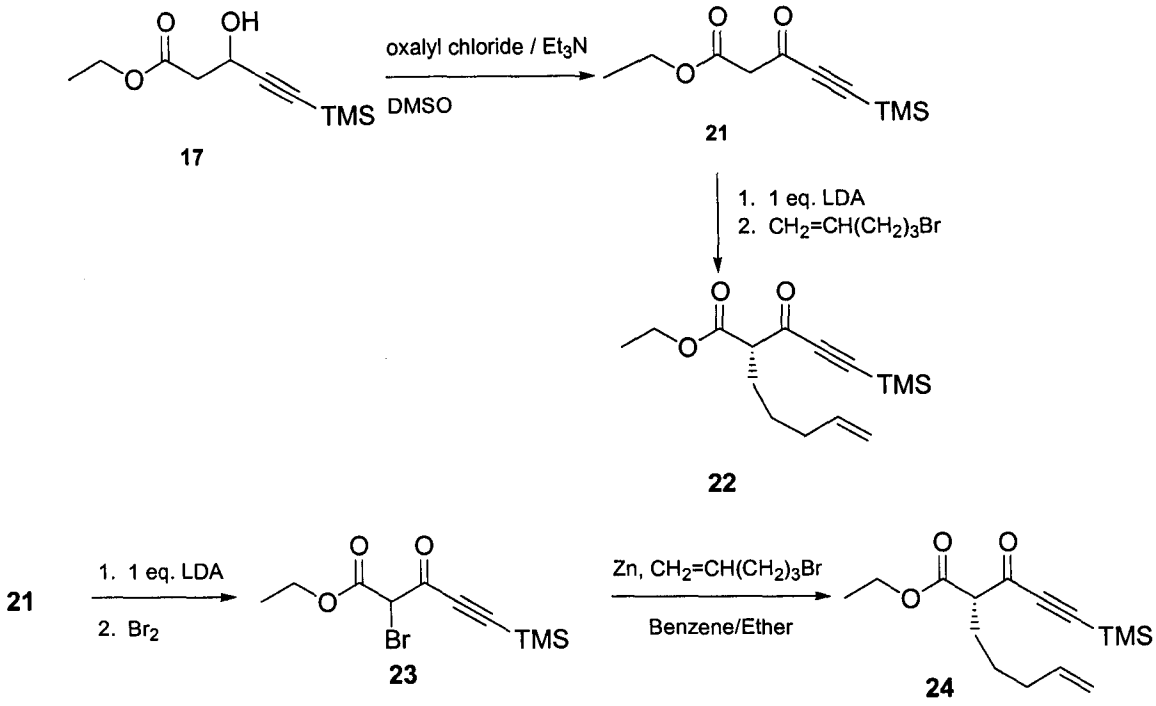


Results

The production of **12** proceeded smoothly as did the reaction to form **17**. However, the production of the enolate ion and its subsequent attack on the 5-bromo-1-pentene was unsuccessful. It is not known if this is due a failure to make the enolate ion or if it is a result of an inability to do a substitution reaction on the primary halide. In the reference paper from Fráter [6], the stereoselective alkylation was accomplished using allyl bromide, which would be a more reactive akylating agent.

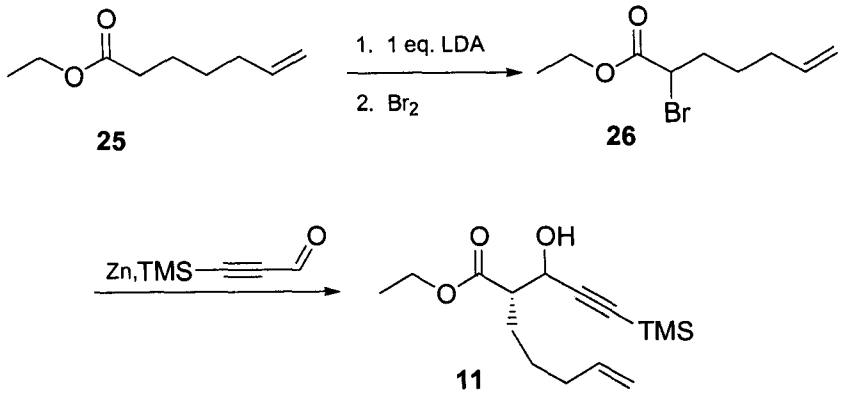
One way to increase the acidity of the hydrogen and thereby improve the production of the enolate ion is to oxidize **17** to the β-keto ester, **21**. After examining several possible pathways [7], it was decided that the Swern oxidation was to be used. If the oxidation were successful, then sodium hydride could be used to deprotonate **21**. Another possibility was to brominate the α-position (**23**), and then use the previously successful activated zinc reaction to give the desired product, **24** (Scheme 4).

Scheme 4. Alternatives for alkylating the β-hydroxy ester



Unfortunately the oxidation was unsuccessful. It was discovered that the compound, ethyl 6-heptenoate (**25**) was commercially available and a new synthesis pathway was planned as detailed in Scheme 5. The first step involves the alpha-bromination of the ester, **25**, to form **26** [8]. This is followed by the insertion of zinc into the carbon-bromine bond to form the organometallic compound, which then attacks the trimethylsilyl propargyl aldehyde to form the desired product **11**.

Scheme 5. Alternative synthesis of 11 using ethyl 6-heptenoate

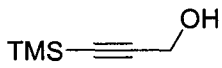


25 26 11

Experimental

Solvents and other reagents were dried when necessary by distillation from sodium metal or CaH_2. All reactions were run under nitrogen atmosphere. All thin layer chromatography was done with Whatman K5F Silica Gel 150 A 250 μm thick plates. All columns were run using Sorbent Technologies 60 Å standard grade silica gel.

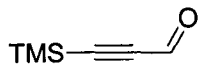
All NMR spectra were taken using the Bruker AC-250 and recorded in parts per million. When chemical shifts are noted, they will follow the format: chemical shift (multiplicity, number of hydrogens, assignment). The multiplicity labels will be abbreviated as follows: s = singlet, d = doublet, t = triplet, m = multiplet.



16

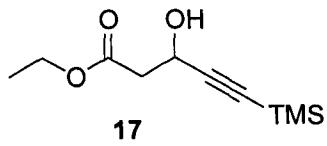
3-trimethylsilyl-2-propyn-1-ol (16). To a stirred solution of 29.3 mL of dry THF was added 77.1 mL (231.2 mmol) of 3.0 M methylmagnesium chloride in THF. 5 mL of propargyl alcohol (4.8 g, 85.6 mmol) (**15**) was diluted in 51.2 mL of THF and added over 1.3 h at 0 °C. The solution was stirred at room temperature for 20 hours, cooled to 0 °C,

and 29.6 mL (25.1 g, 231.2 mmol) of trimethylsilyl chloride was added over 20 minutes. The solution was stirred while refluxing for 3 hours. Large amounts of a white solid ($MgCl_2$) were observed. The solution was cooled to 0 °C and then stored overnight in the freezer. The solution was warmed to 0 °C and 95.4 mL of 1.4 M sulfuric acid was added dropwise. The solution was stirred for 5 minutes and then diluted with 128 mL of ether. The layers were separated and the aqueous layer was extracted twice with 99 mL of ether. The combined organic layers were washed with 100 mL of water and 100 mL of brine. The ether was then dried with anhydrous magnesium sulfate and concentrated in vacuo. The golden oil was distilled (67 °C, 15 mmHg) to afford 8.95 g (82 %) of the alcohol as a colorless oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.27 (s, 2H, CH_2), δ 2.26 (s, 1H, OH), δ 0.18 (s, 9H, $SiCH_3$).



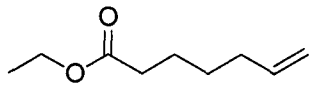
12

3-trimethylsilyl-2-propyn-1-al (12). To a solution of 8.95 g (70.9 mmol) of trimethylsilyl propynol (**16**) in 294 mL of methylene chloride was added 30.57 g (141.8 mmol) of PCC. The mixture was stirred for 20 hours and then filtered through a pad containing ½ inch silica gel. The filtrate was stirred with 18 g of activated charcoal for 5 minutes. It was then filtered through a ¾ inch pad of 1:1:1 silica gel, Celite, and magnesium sulfate. The solution was then filtered through a ¾ inch pad of silica gel. The residue was concentrated in vacuo to yield 5.64 g (64%). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.17 (s, 1H, HC=O), δ 0.27 (s, 9H, CH_3).



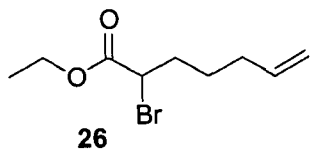
17

3-hydroxy-5-trimethylsilanyl-pent-4-ynoic acid ethyl ester (17). To 1.30 g of activated zinc in 2.43 mL of a 2:1 mixture of benzene and ether was added a mixture of 1.24 g (10 mmol) of **12** and 1.70 g (10.2 mmol, 1.13 mL) of ethyl bromoacetate in 1.62 mL of a 2:1 mixture of benzene and ether. This was done dropwise over 10 minutes with periodic heating. At the end of the addition, the solution was boiled for 0.5 hour. The reaction mass was cooled to 0 °C and was treated with a 10% sulfuric acid solution. The layers were separated and the aqueous layer was extracted twice with benzene. The organic layers were combined, washed with a 5% sodium bicarbonate solution and water to a neutral solution and concentrated in vacuo. This yielded 1.33 g of material representing a 62% yield. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.75 (d, 1H, CHOH), δ 4.18 (m, 2H, OCH_2), δ 3.11 (d, 1H, OH), δ 2.73 (d, 2H , $OOCCH_2$), δ 1.28 (t, 3H, CH_3), δ 0.17 (s, 9H, $SiCH_3$).



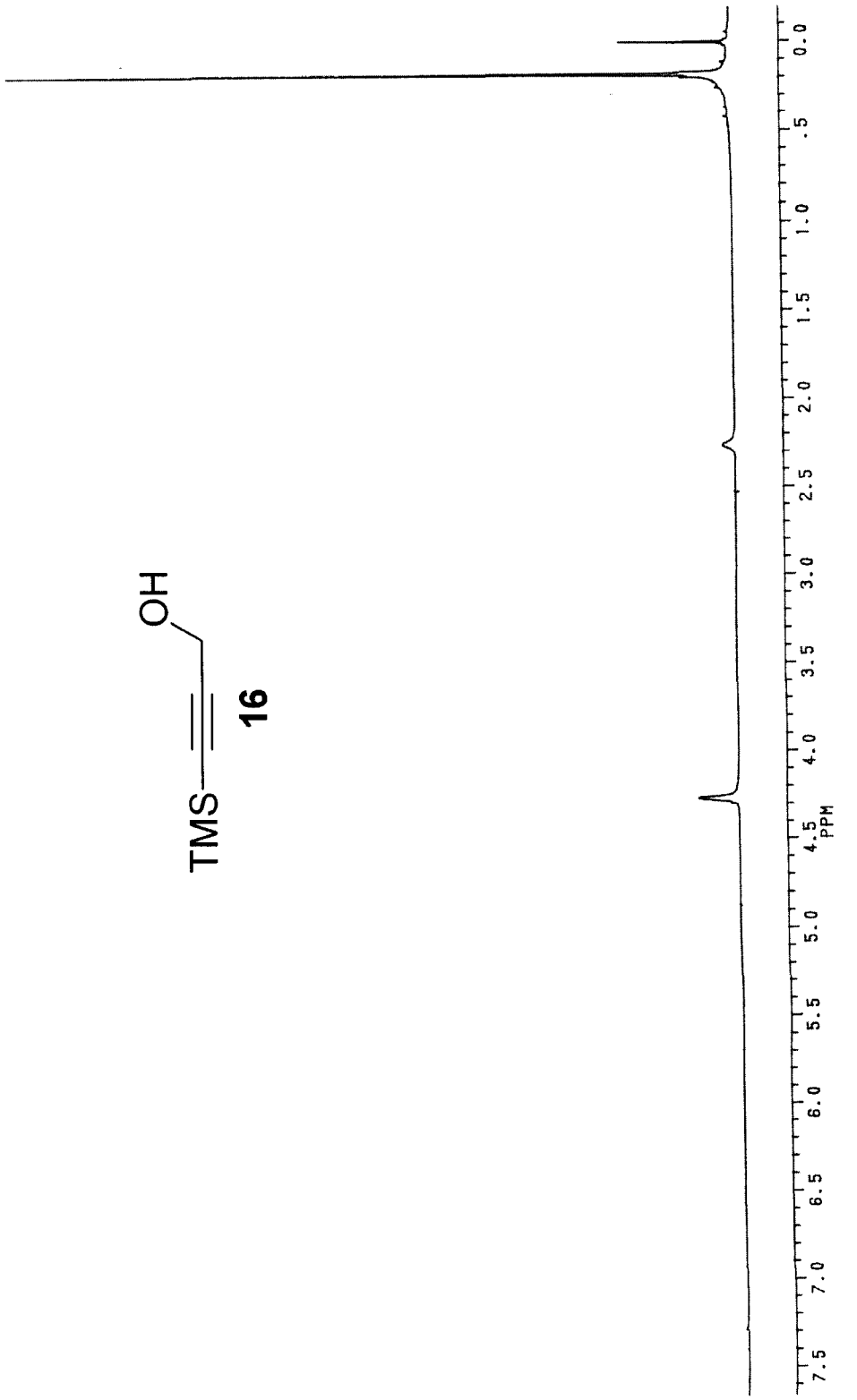
25

Ethyl 6-heptenoate (25). ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.8 (m, 3H, $CH=CH_2$), δ 4.1 (m, 2H, CH_2O), δ 2.3 (t, 2H, $OOCCH_2$), δ 2.0 (m, 2H, $CH_2C=C$), δ 1.6 (m, 2H, $OOCCCH_2$), δ 1.44 (m, 2H, $CH_2CC=C$), δ 1.25 (t, 3H, CH_3).



26

Ethyl 2-bromo-6-heptenoate (26). To a solution of 1.53 mL (10.9 mmol) of diisopropylamine and 27.5 mL THF at -78 °C was added 6.25 mL (10 mmol) of n-BuLi in hexanes (1.6 M) over 30 minutes. The solution was stirred for 15 minutes at -78 °C, warmed to 0 °C and stirred for 40 minutes, and then cooled to -78 °C. Then 1.76 mL (1.56 g, 10 mmol) of ethyl 6-heptenoate (**25**) was added dropwise over 10 minutes. The solution was stirred further for 2 hours and was then allowed to warm to room temperature. The enolate solution was then cooled to dry ice temperature. A solution of 0.51 mL (10 mmol) bromine in 10 mL of THF was then added dropwise to the enolate solution over 15 minutes. 2 mL of concentrated HCl were injected over 2 minutes and the solution was allowed to warm to room temperature. The solution was washed twice with 12 mL portions of water with enough thiosulfate to remove the bromine color. The organic portion was then concentrated in vacuo to yield 1.31 g (56%) of yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.8 (m, 3H, $CH{=}CH_2$) δ 4.12 (m, 2H, CH_2O) δ 3.4 (t, 1H, CHBr) δ 2.1 (m, 2H, $CH_2C{=}C$) δ 1.6 (m, 2H, CH_2CBr) δ 1.42 (m, 2H, $CH_2CC{=}C$) δ 1.25 (t, 3H, CH_3).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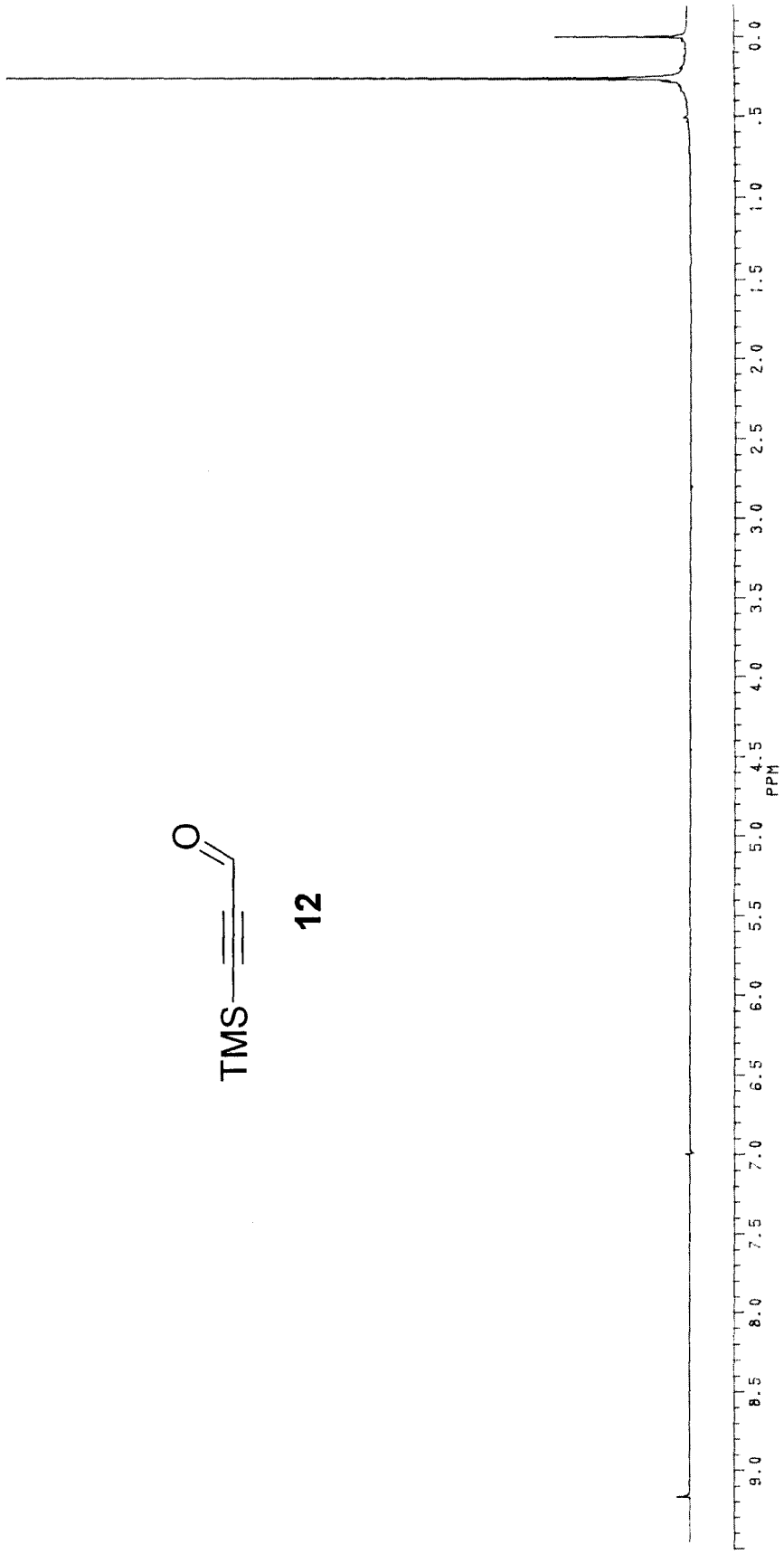
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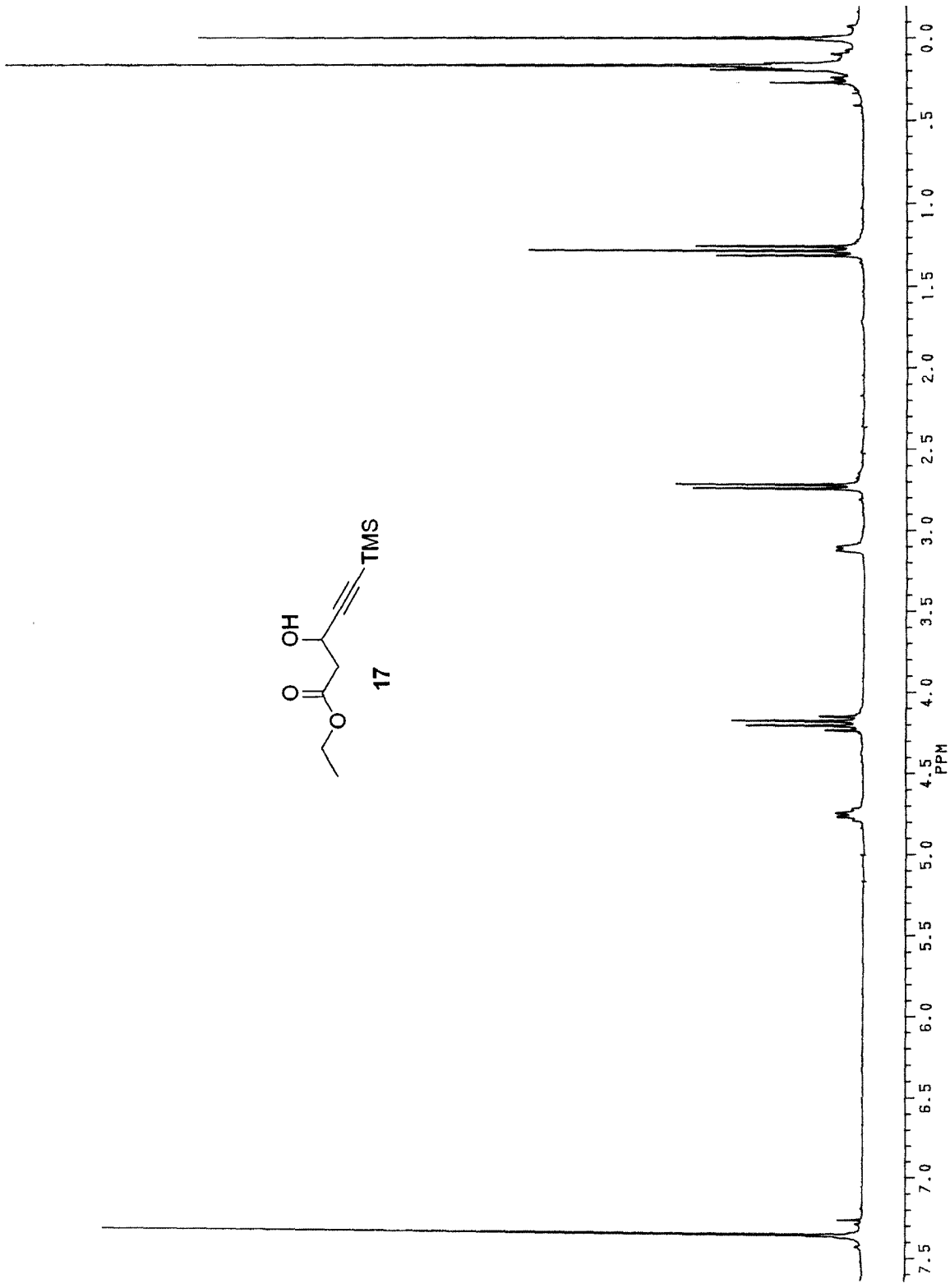
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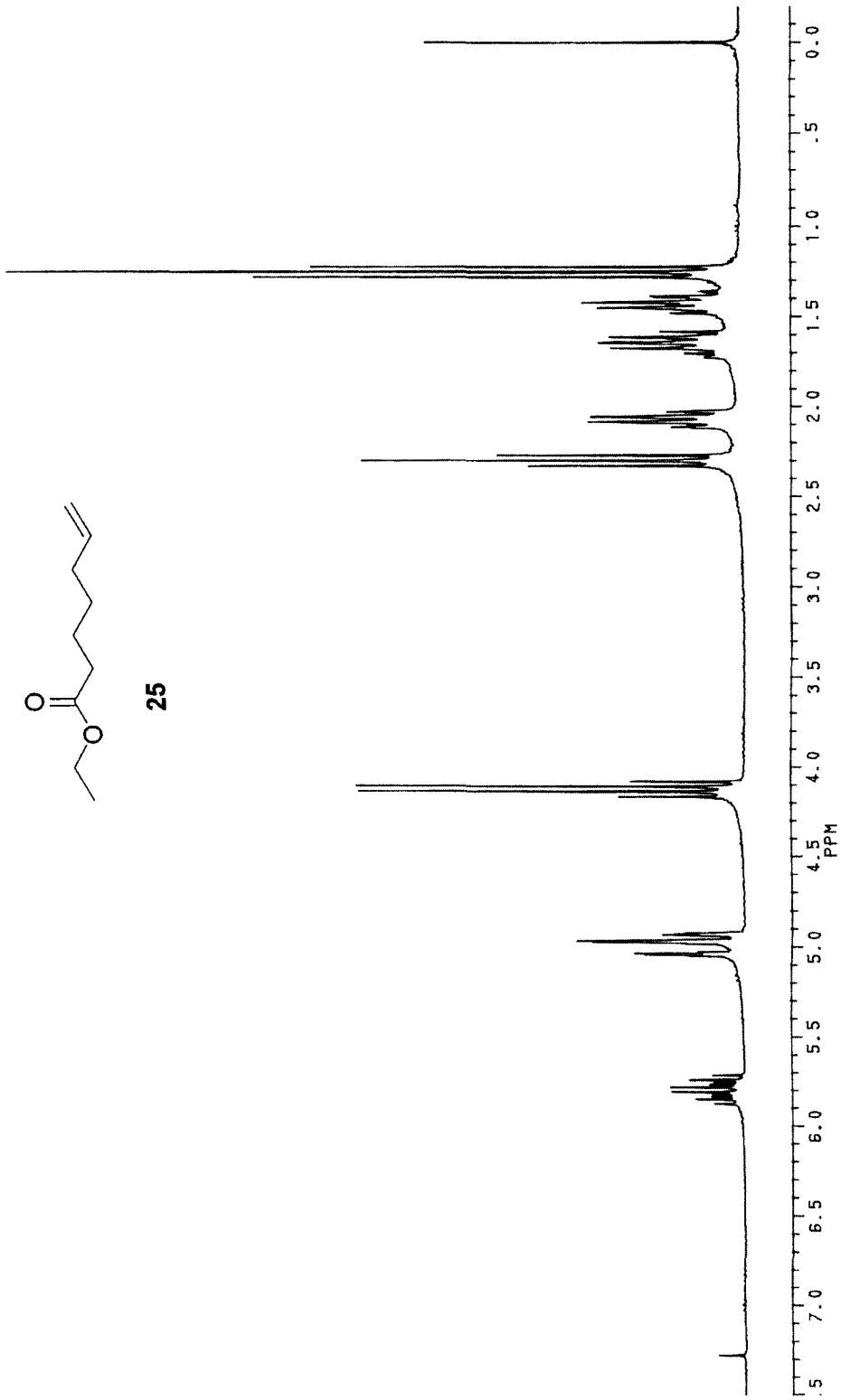
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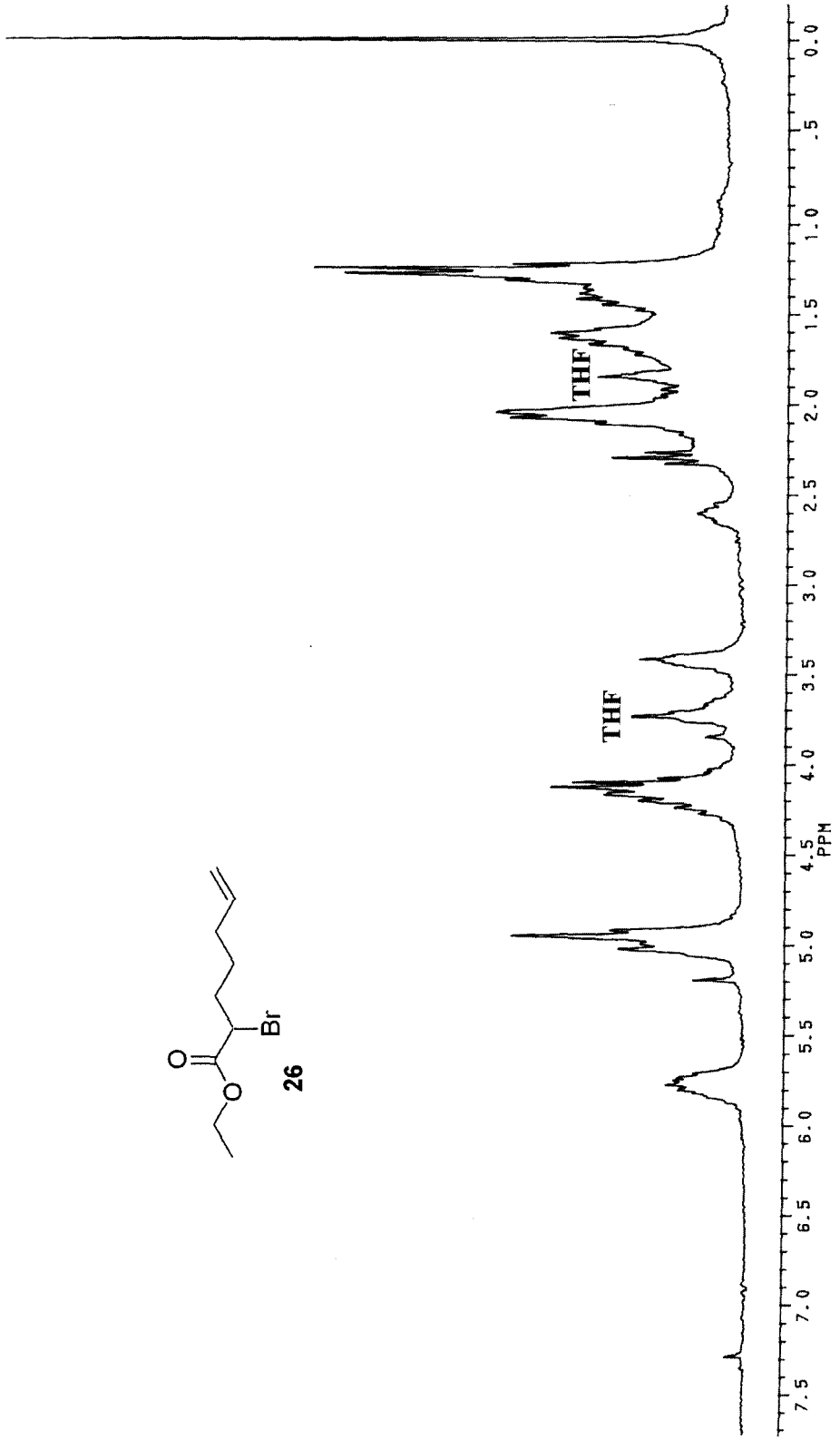

26

349 Table 1 Means of Variables in the Study

Variable	Mean	Range
Age (years)	27.9+/-5.7	18-39
Income (dollars)	$25,000+/-15,000	$0->$50,000
Parity	1.89+/-1.3	1-8
Milk SIgA (mg/ml)	497.3+/-317.4	245.5-2168.9
Serum γ-IFN (pg/ml)	10.34+/-12.6	0-50
Serum Cortisol (ng/ml)	168.5+/-87	33.4-411
Serum IL-2 (pg/ml)	6.65+/-9.4	.05-53.1
Serum IL-10 (pg/ml)	288.3+/-86.7	7.4-425.7
Serum IL-6 (pg/ml)	48.6+/-63.9	.2-290
Serum TNF-α (pg/ml)	10.01+/-24.5	0-160.3
Cohen Perceived Stress Score	28.7+/-7.8	15-55
ISLE Negative Events	32+/-15.8	7-71
[illegible]		
POMS-anger/hostility	8.35+/-7.56	0-45
Infection SCL score	6.6+/-6.8	0-33

350

References:

1. Hecker, E. *Cancer Res.* **1968**, *28*, 2338.
2. Zechmeister, K.; Brandl, F.; Hoppe, W.; Hecker, E.; Opferkuch, H. J.; Adolf, W. *Tetrahedron Lett.* **1970**, 47, 4075.
3. Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y.T. *J. Am. Chem. Soc.* **2002**, 124, 9726.
4. Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, 125, 1498.
5. a) Erdik, E. *Tetrahedron.* **1987**, 43, 2203.
   b) Newman, M. S.; Evans, D. F.; James, J. R . *J. Am. Chem. Soc.* **1955**, 77, 946.
   c) Panchenko, S. I.; Bychkova, N. A.; Yurevich, G. P.; Zotchick, N. V.; Rubtsov, I. A. *Zh. Org. Khim.* **1982**, 18, 2489.
6. Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1981**, 40, 1269.
7. Smith, A. B., III; Levenberg, P. A. *Synthesis.* **1981**, 567.
8. Rathke, M. W.; Lindert, A. *Tetrahedron Lett.* **1971**, 43, 3995.